DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103949/5002

AUG 0 7 2001

Nicholas J. Pelliccione, Ph.D.
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Pelliccione:

Your request to supplement your biologics license application for Peginterferon alfa-2b (PEG-Intron) to include combination therapy with Ribavirin, USP (Rebetol), for the treatment of chronic hepatitis C has been approved.

We acknowledge your agreement to conduct post-marketing studies in patients with chronic hepatitis C and to provide additional information as described in your August 7, 2001, letter and as outlined below:

1. To assess the safety and efficacy of alternative dose regimens of Ribavirin when used in combination therapy with Peginterferon alfa-2b, by directly comparing the safety and efficacy of a fixed dose (800mg) of Ribavirin to variable, weight-based doses of Ribavirin. A 3,000 patient study is underway under ——— and patient accrual will be completed by December 1, 2001. An interim (24-week) analysis will be completed by May 1, 2002, and an interim report will be submitted by July 15, 2002. This study will be completed by May 1, 2003, and a final report (with revised labeling if applicable) will be submitted by December 1, 2003.

2. To assess the safety and efficacy of alternative dose regimens of Peginterferon alfa-2b when used in combination with Ribavirin in patients with chronic hepatitis C genotype 1, by directly comparing 1.0 μg/kg and 1.5μg/kg doses of Peginterferon alfa-2b. In this study either a fixed (800 mg) or weight-based dose of Ribavirin will be used.

   a. If CBER concurs that further analyses of currently available data from study ——— show that 24-week virologic response rates are predictive of sustained response rates, the dose of Ribavirin to be used in this study will be based on the interim results of the study described in item 1 above. The final protocol for this study will be submitted to CBER by March 30, 2002. Patient accrual will be completed by July 30, 2003, the study will be completed by December 20, 2004, and a final study report (with revised labeling if applicable) submitted by May 15, 2005.

b. Alternatively, a fixed dose of 800 mg Ribavirin will be used in this study. The final protocol will be submitted to CBER by October 30, 2001. Patient accrual will be completed by October 30, 2002, the study will be completed by April 30, 2004, and a final study report (with revised labeling if applicable) will be submitted to CBER by November 30, 2004.

3. To provide sufficient data to determine whether a 6-month regimen of Peginterferon alfa-2b in combination with Ribavirin is a safe and effective alternative to a 12-month regimen in patients with favorable prognostic factors.

a. Schering will evaluate the effect of duration of treatment in a minimum of 1,000 patients derived from the study described in item 1 above. If less than 1,000 patients are available from that study Schering will extend enrollment of that trial or initiate a new 1,000 patient study. Patient accrual will be completed by December 1, 2001, the study will be completed by May 1, 2003, and a final study report (with revised labeling if applicable) will be submitted to CBER by December 1, 2003.

b. Schering will provide data from the ———————————— ———————————— . Patient accrual will be completed by April 2, 2003, the study completed by March 3, 2004, and a final study report submitted to CBER by July 15, 2004.

4. To determine the relative bioavailability of Ribavirin capsules (200 mg X 2) when administered with a high fat meal or a non-fat meal relative to the fasted state. The final protocol will be submitted by December 15, 2001. Patient accrual will be completed by March 1, 2002, the study completed by July 1, 2002, and the final report submitted by December 20, 2002.

5. To provide the final study report for the p53 carcinogenicity study that is being performed as listed in CDER's approval letter for NDA 20-903 and per subsequent discussions with the Division of Antiviral Drug Products. A final report will be submitted by July 31, 2002.

Pursuant to 21 CFR Part 208, FDA has determined that Peginterferon alfa-2b alone or in combination with Ribavirin capsules poses a serious and significant public health concern requiring the distribution of a Medication Guide. Distribution of a Medication Guide is necessary for safe and effective use of this product. FDA has determined that Peginterferon alfa-2b is a product for which patient labeling could help prevent serious adverse effects and inform the patient of serious risks relative to benefit that could affect their decisions to use, or

continue to use the product. See 21 CFR 208.1. FDA hereby approves the Medication Guide you submitted August 7, 2001. In accordance with 21 CFR 208, you are responsible for ensuring that this Medication Guide is available for every patient who is dispensed a prescription for this product. In addition, you are responsible for ensuring that the label of each package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. Please note that the Medication Guide must be printed in a minimum of 10 point high text, as described in 21 CFR 208.20.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

This information will be included in your biologics license application file.

Sincerely yours,

Karen D. Weiss, M.D.
Director
Division of Clinical Trial
Design and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research